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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/845,512	04/30/2001	K. Roger Aoki	D2935CON	3427

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EXAMINER	
HAYES, ROBERT CLINTON	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/845,512	AOKI ET AL.	
	Examiner	Art Unit	
	Robert C. Hayes, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/9/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Oath/Declaration

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify the mailing address (P.O.Box) of each inventor. A mailing address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing address should include the ZIP Code designation. The mailing address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

Res Judicata

2. Claims 11 & 12 are rejected on the grounds of *res judicata* (MPEP 706.03 (w)), as the issues presented by these claims are the same as those decided by the Board of Appeals and Interferences in a decision dated November 28, 2000 (*Ex parte* Aoki et al., Appeal No. 1997-2367).

Claim Objections

3. Claim 13 is objected to because of the following informalities:

The recitation in claim 13 for "(b) administering... botulinum toxin type E to the human before the human exhibits a substantially reduced response to the administration of botulinum toxin type A ***and B***" appears to be a typographical error since no antecedent basis exists in step

(a) for administration of type B. Appropriate correction is required. Otherwise, this limitation is rejected under both new matter and 112, second *pp*, as indicated below.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. .

No proper antecedent basis nor conception in context with that described within the specification at the time of filing the instant application is apparent for the recitation in new claim 13 for "(b) administering… botulinum toxin type E to the human *before* the human exhibits a substantially reduced response to the administration of botulinum toxin *type A and B*"; thereby, constituting new matter.

5. Claims 11 & 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of a "*substantially* reduced response..." is indefinite because it is unclear when a "substantially reduced response" is no longer a "substantially reduced response". In other words, the term "substantially reduced response" in claims 11 & 13 is a relative term which renders the claim indefinite. The term "substantially reduced response" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention; especially when what constitutes the metes and bounds of a "reduced response" is unknown and not defined within the claims. Lastly, no antecedent basis exists for the recitation of "and B" in claim 13(b) because no administration of type B toxin is recited in step 13(a).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ludlow et al. (IDS Ref #ac), in view of Simpson et al. (IDS Ref #ag) and Janovic et al. (IDS Ref #ae).

Ludlow et al teach the treatment of neuromuscular disorders such as torticollis and oromandibular dystonia (movement disorders characterized by muscle spasm/spasmodic activity) by intramuscular injection of botulinum toxin type F after the patients had already been treated with botulinum toxin type A and had developed neutralizing antibodies to the type A toxin (i.e., as manifested as a reduced response to type A toxin; pages 349-350; as it relates to claims 11 & 12). However, Ludlow et al do not teach administration of botulinum toxin type E after administration of botulinum toxin type A, nor administration of type E toxin before a reduce response to type A toxin is observed.

Simpson et al teach that all of the botulinum serotypes A, B, C1, C2, D, E, F and G are produced by the same species of bacterium, and review of their pharmaceutical activities. In particular, all of the botulinum serotypes block acetylcholine release for nerve endings, and each of the serotypes are taught to be "antigenically distinct" (e.g., pages 155-156). Therefore, it is reasonable to expect that administration of any of the serotypes would produce the same physiological effect of blocking cholinergic neuronal transmission by "interrupt[ing] transmission at the muscle end organ" (i.e., reduced muscle spasm/twitch; pages 163- 164 & 167). Accordingly, because the serotypes differ antigenically, antibodies developed against a first administered serotype would not be expected to block the activity of a second serotype at

the cholinergic receptor. This is consistent with the teachings of Ludlow et al., who teach that the advantage of administering a second serotype toxin is to overcome the reduced responsiveness to the first toxin.

Further consistent with both the teachings of Ludlow et al and Simpson et al, Jankovic et al teach that botulinum toxin is used for the treatment of neuromuscular disorders such as muscle spasm (e.g., Table 1, page 1187). Jankovic et al also teach that "blocking" antibodies develop to the toxin, which cause patients to be nonresponsive to the toxin (page 1189, column 1). Jankovic et al then conclude that "[i]t is likely that patients with antibodies against botulinum toxin will respond to injections with other boltulinum toxins that are immunologically distinct from type A" (page 1189, column 1).

Thus, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to use Ludlow's methods of administering botulinum toxin type A to treat movement disorders characterized by muscle spasm, followed by administration of another botulinum toxin, such as type E as taught by Simpson or Jankovic, in order to continue reducing muscle spasms in these patients. It is emphasized that both Simpson et al and Jankovic specifically suggest administration another botulinum serotype toxin after patients become nonresponsive to a first botulinum toxin (i.e., type A). In that Ludlow teach that a reduced response to type A toxin probably is due to development of neutralizing antibodies to the type A toxin, administration either before or after a "substantially reduced response" in clinical symptoms would be obvious, in order to maintain a positive clinical response for the patient.

It is noted that in contrast to Applicants' assertions on page 6 of the preliminary amendment, no copies of the Tsuzunki et al., Siegel, Ferreira or Bonventre et al references were submitted for the Examiner's consideration. Nor have any of these references been submitted in a properly filed IDS.

Note that the IDS filed 10/09/01 has been fully considered by the Examiner. However, those references crossed out will not be published in any issued patent due to the ambiguity of the citations.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (571) 272-0885. The examiner can normally be reached on Monday through Thursday, and alternate Fridays, from 8:30 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (571) 272-0887. The fax phone number for this Group is (703) 872-9306.

Robert C. Hayes, Ph.D.
June 22, 2004
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